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Under-utilization of evidence-based drug treatment in patients with heart failure is only partially explained by dissimilarity to patients enrolled in landmark trials: a report from the Euro Heart Survey on Heart Failure

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Abstract: Aims Surveys on heart failure management suggest under-utilization of life-saving evidence-based treatment. Evidence-based medicine and clinical guidelines are based on the results of randomized controlled trials. Therefore, we investigated how patients who fulfilled the enrolment criteria of randomized trials were treated in real life. **Methods and results** We selected three large placebo-controlled trials of patients with chronic heart failure, in which ACE-inhibitors (ACE-Is), -blockers, and spironolactone proved to be safe and effective. The major enrolment criteria of trials were identified and applied to patients enrolled in the Euro Heart Survey on Heart Failure to identify the proportion of patients eligible for treatment and also treated appropriately. Of the 10 701 patients who were enrolled in the Euro Heart Survey on Heart Failure, only a small percentage (13%) would have qualified for participation in at least one of the selected trials. Patients who fulfilled enrolment criteria of the identified trials were more likely to be treated with ACE-Is (83% of SOLVD-eligible patients), -blockers (54% of MERIT-HF-eligible patients), and aldosterone antagonists (43% of RALES-eligible patients) than trial-ineligible patients. Almost half of SOLVD-eligible patients who were treated with ACE-Is received the target dose as recommended in the guidelines, but only <10% of MERIT-HF eligible patients who were treated with -blockers received the target dose. **Conclusion** ACE-Is are widely utilized but given in lower doses than proven effective in clinical trials. -Blockers are underused and given in lower doses to patients who fulfil the enrolment criteria of relevant landmark trials

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Under-utilization of evidence-based drug treatment in patients with heart failure is only partially explained by dissimilarity to patients enrolled in landmark trials: a report from the Euro Heart Survey on Heart Failure

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Aims Surveys on heart failure management suggest under-utilization of life-saving evidence-based treatment. Evidence-based medicine and clinical guidelines are based on the results of randomized controlled trials. Therefore, we investigated how patients who fulfilled the enrolment criteria of randomized trials were treated in real life.

Methods and results We selected three large placebo-controlled trials of patients with chronic heart failure, in which ACE-inhibitors (ACE-Is), β -blockers, and spironolactone proved to be safe and effective. The major enrolment criteria of trials were identified and applied to patients enrolled in the Euro Heart Survey on Heart Failure to identify the proportion of patients eligible for treatment and also treated appropriately. Of the 10 701 patients who were enrolled in the Euro Heart Survey on Heart Failure, only a small percentage (13%) would have qualified for participation in at least one of the selected trials. Patients who fulfilled enrolment criteria of the identified trials were more likely to be treated with ACE-Is (83% of SOLVD-eligible patients), β -blockers (54% of MERIT-HF-eligible patients), and aldosterone antagonists (43% of RALES-eligible patients) than trial-ineligible patients. Almost half of SOLVD-eligible patients who were treated with ACE-Is received the target dose as recommended in the guidelines, but only <10% of MERIT-HF eligible patients who were treated with β -blockers received the target dose.

Conclusion ACE-Is are widely utilized but given in lower doses than proven effective in clinical trials. β -Blockers are underused and given in lower doses to patients who fulfil the enrolment criteria of relevant landmark trials.

Introduction

Chronic heart failure (CHF) is a major health problem with a high morbidity and mortality.^{1,2} Over the last two decades, major advances have occurred in the treatment of heart failure patients. Randomized clinical trials (RCTs) showed that ACE-inhibitors (ACE-Is),^{3–5} β -blockers,^{6–8} and aldosterone antagonists^{9,10} could reduce morbidity and mortality in patients with heart failure. Guidelines have been established to support physicians in clinical decision-making in this rapidly evolving field.^{11–14} In these guidelines, RCTs

are accorded the highest level of evidence. However, although physicians are increasingly encouraged to apply these guidelines in their practise, it is repeatedly observed that a considerable proportion of heart failure patients do not receive evidence-based treatment.^{15–20}

Several factors may explain the reported under-utilization of evidence-based treatment, such as lack of knowledge, lack of expertise in the use of such drugs, lack of time, and economic restraints. Another issue that is often brought forward is the limited generalizability (external validity) of RCTs as it is emphasized that these trials usually enrol highly selected patients.^{21–27} In reality, clinicians may be right to withhold treatment in patients who do not fulfil the inclusion and exclusion criteria used to select

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patients for RCTs. Information is scarce on whether evidence-based treatment is offered more often to patients who match the profile of patients who were enrolled in RCTs when compared with those who were not.

Therefore, we investigated what proportion of patients with suspected or known heart failure who enrolled the Euro Heart Survey on Heart Failure¹⁹ was eligible for participation in the largest placebo-controlled trials of ACE-Is, β -blockers, and aldosterone antagonists, which demonstrated the effectiveness and safety of these agents. We then analysed what proportion of patients met or did not meet these criteria, and whether they were treated according to the guidelines.

Methods

Euro Heart Survey on Heart Failure

Between March 2000 and May 2001, 46 788 patients from 115 hospitals in 24 ESC member countries were screened for enrolment in the Euro Heart Survey on Heart Failure.^{19,20,28} Briefly, all consecutive discharges and deaths from general medical, cardiology, or cardiac surgery wards were screened over a 6-week period. Patients who fulfilled one or more of the following four criteria were enrolled: (i) a clinical diagnosis of heart failure during the admission; (ii) a diagnosis of heart failure recorded at any time in the last 3 years; (iii) administration of a loop diuretic for any reason other than renal failure in the 24 h before death or discharge; and/or (iv) pharmacological treatment for heart failure or ventricular dysfunction in the 24 h before death or discharge. Information about characteristics, diagnosis, and treatment on 10 701 enrolled patients was collected.^{19,20}

Trial selection

To compare patients in the RCTs with those enrolled in the Euro Heart Survey, we selected the largest placebo-controlled trials in which ACE-Is, β -blockers, and aldosterone antagonists had been shown to reduce mortality in patients with CHF. These were SOLVD (ACE-I), MERIT-HF (β -blocker), and RALES (aldosterone antagonist).^{4,6,9} In addition, we compiled the tabulated patient characteristics, as presented in the main results papers of these trials

('pooled RCTs'). Data were pooled if certain characteristics were available in at least two trials, either by reports of the actual counts or by percentages.

The major enrolment criteria for these trials were extracted from the main articles and summarized in Table 1. The most important inclusion criterion in these trials was the left ventricular ejection fraction (LVEF). Important exclusion criteria were renal failure, respiratory diseases (including asthma and chronic obstructive respiratory disease during the index admission), obstructive valvular heart disease, acute coronary syndrome during the index admission, and limited life expectancy by other diseases. Furthermore, we identified pacemakers, ventricular assist devices, planned heart transplantation, congenital heart disease, laboratory values (i.e. creatinine and potassium), and administered cardiovascular drugs (i.e. calcium antagonists and amiodarone) as exclusion criteria in some of these trials.

Identifying trial-eligible survey patients

On the basis of the earlier mentioned criteria, survey patients with identifiable contraindications (i.e. age, co-morbidity, etc.) or a higher LVEF than allowed in the RCTs were classified as trial-ineligible patients. Trial-eligible patients were those who had no contraindications and fulfilled the LVEF criterion, whereas the remaining patients were classified as 'other survey patients'. In these patients, no quantitative measurement of the LVEF was available and no contraindications were observed. It should be noted, however, that defining patients from clinical practice as trial eligible or trial ineligible is, by necessity, crude.

Within the subgroups of SOLVD-, MERIT-HF-, and RALES-eligible patients, we analysed the administered dose of ACE-Is and β -blockers on the day of discharge or the day before death when compared with the target dose. We defined the target dose as the minimum recommended maintenance dose or higher approved for the treatment of heart failure in Europe.¹³ For ACE-Is, this is 75 mg for captopril, 20 mg for enalapril, 5 mg for ramipril, 5 mg for lisinopril, and 4 mg for perindopril. For β -blockers, dosages were 150 mg for metoprolol, 50 mg for atenolol, 50 mg for carvedilol, and 10 mg for bisoprolol.

Statistical analysis

Descriptive statistics included percentages for dichotomous variables and medians with corresponding 25th and 75th percentiles

Table 1 Major inclusion and exclusion criteria of selected trials

	SOLVD 1991	MERIT-HF 1999	RALES 1999
Drug comparison	Enalapril	Metoprolol	Spironolactone
Number of participants	2569	3991	1663
Major enrolment criteria			
Age	≤ 80	40–80	—
NYHA	—	II–IV	III–IV
LVEF	≤ 0.35	≤ 0.40	≤ 0.35
Renal failure (creatinine level)	Exclude (>2.0 mg/dl)	—	Exclude (>2.5 mg/dl)
Severe pulmonary disease	Exclude	Exclude	—
Severe valve disease	Exclude	—	Exclude
ACS (recent)	Exclude	Exclude	Exclude
Limited life-expectancy	Exclude	Exclude	Exclude
ACE-I therapy	Exclude	Mandatory	Mandatory
β -Blocker therapy	—	Exclude	—
Calcium antagonists	—	Exclude	—
Diuretics	—	Mandatory	Mandatory ^a
Amiodarone	—	Exclude	—

NYHA, New York Heart Association; ACS, acute coronary syndrome.

^aPotassium-sparing diuretics excluded.

for continuous variables. Differences between trial-eligible and trial-ineligible patients were analysed by χ^2 and Mann-Whitney *U*-test or Kruskal-Wallis test as appropriate. For all tests, a *P*-value of <0.05 (two-sided) was considered statistically significant. All analyses were performed with SPSS statistical software version 12.0.

We acknowledge the fact that patients who died during the initial hospitalization could have a worse clinical profile and consequently influence the results. Therefore, we repeated the analyses excluding patients who did not survive to hospital discharge. As the results of the analyses with and without patients who died during the initial hospitalization were highly consistent, we report our original choice on the basis of the total survey population.

Results

As shown in *Figure 1*, only small proportions of patients enrolled in the Euro Heart Survey on Heart Failure would have qualified for participating in the SOLVD (9%), MERIT-HF (5%), and RALES (7%) trials. Exclusion criteria such as age and identified contraindications were the most important reasons for not classifying patients as trial-eligible. In addition to this, we were unable to classify a considerable proportion of patients as trial-eligible because of the absence of a LVEF measurement. Similarly, patients were only considered MERIT-HF eligible when they were treated with a diuretic and ACE-I (or angiotensin-II-antagonist) and RALES-eligible when treated with an ACE-I and loop diuretic.

Overall, 1346 patients (13%) would have qualified for participating in at least one of the three selected trials (*Table 2*). Within this pooled trial-eligible population, 256 patients would have qualified for all three trials and 692 patients would have qualified for at least two trials. These trial-eligible patients show considerable differences when compared with those who did not qualify for trial participation. Consistent with the results of clinical trials, the majority of trial-eligible patients were men (75%). It should be noted, however, that almost half (47%) of the survey participants were women, but they represented only 27% of those with a LVEF ≤ 0.40 . Ischaemic heart disease was observed less frequently in patients without exclusion criteria but unknown LVEF (other survey patients) when compared with trial-eligible and trial-ineligible patients. Limited life expectancy was defined as any known malignancy and observed in 16% of the trial-ineligible patients.

Most patients who fulfilled trial criteria were treated with ACE-Is (83–100%) (*Table 3*). Almost two-third of all trial-eligible patients were treated with at least half of the target dose and 40–50% received the minimum regulatory recommended dose.¹³ As the recommended maintenance doses of ACE-Is in the guidelines are given as dose ranges, we repeated the analysis using the maximum regulatory recommended doses. This corresponded to 50% of SOLVD and 57% of MERIT-HF and RALES eligible patients who were treated with at least half of this higher target dose. With regard to β -blockers, 54% of MERIT-eligible patients received a β -blocker, of whom in 20% at least half of the target dose was given, whereas only 6% received the target dose. Aldosterone antagonists were given to a large minority (43%) of heart failure patients, fulfilling the enrolment criteria of the RALES trial. Of all survey patients, 3658 (34% of all patients or 54% of those who underwent imaging) had evidence of a left ventricular systolic dysfunction (LVSD), defined as a LVEF ≤ 0.40 or a report of moderate

or severe LVSD on echocardiography. Of these patients, 78% was treated with an ACE-I, 46% with a β -blocker, and 29% with an aldosterone antagonist. In the absence of renal failure and asthma ($n = 2762$, 26%), slightly more patients were given ACE-Is (80%) and β -blocker (48%), whereas treatment with aldosterone antagonists remained 29%.

The incidence of all-cause mortality during the 12-week follow-up period of hospital survivors was lower in patients who received at least 50% of the target dose of ACE-Is or β -blockers in, respectively, SOLVD (4.0 vs. 8.7%) and MERIT-HF (2.9 vs. 8.8%) eligible patients (*Table 4*). This beneficial effect of treating patients with $\geq 50\%$ of the target dose was also observed in patients who did not fulfil the study criteria of the selected trials.

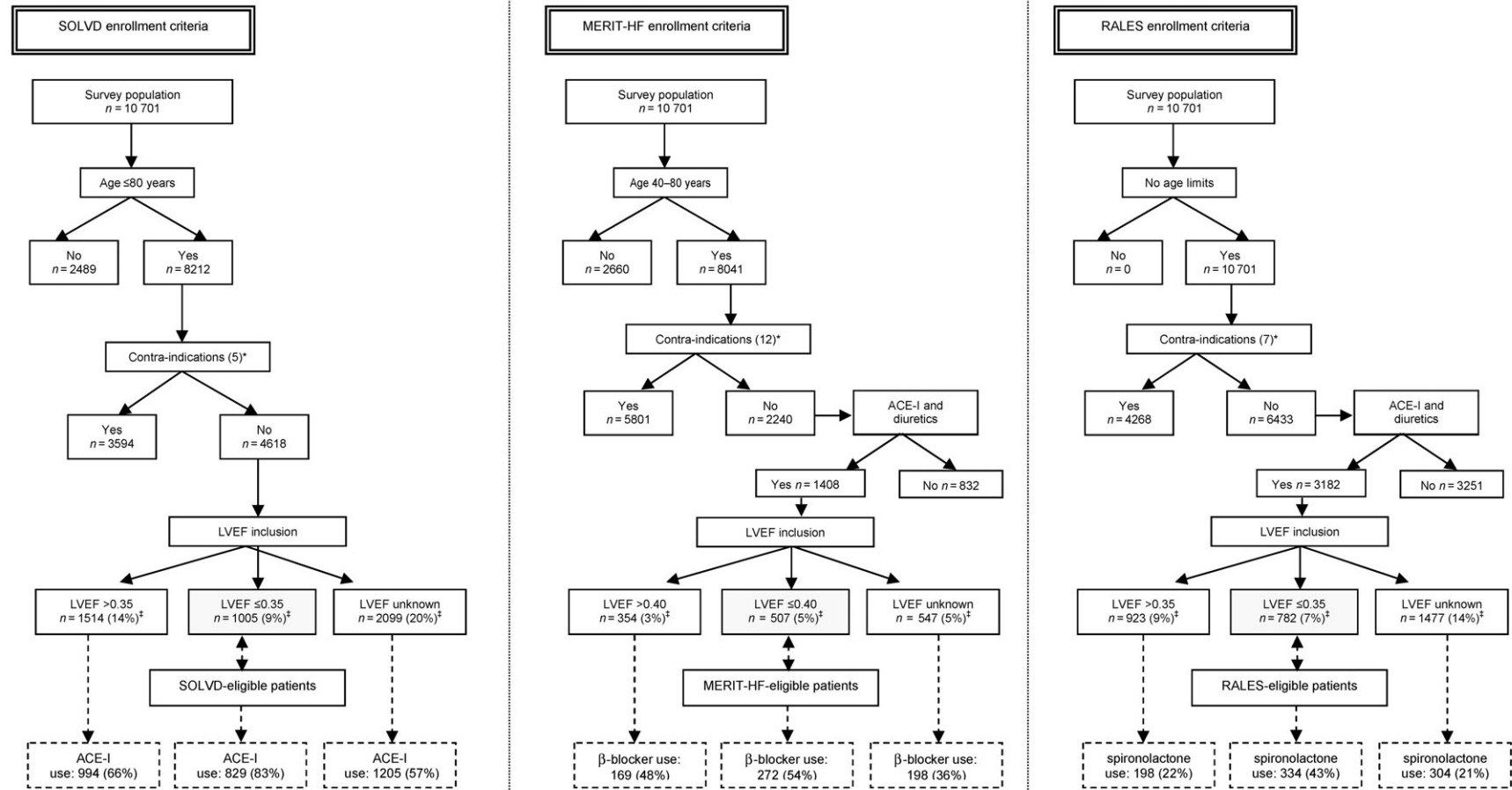
Discussion

The present study clearly revealed that the patients enrolled in RCTs are a highly selected group. Only a small proportion of patients enrolled in the Euro Heart Survey on Heart Failure would have fulfilled the entry criteria of at least one of the selected landmark trials. In this subgroup of trial-eligible patients, hardly one-half were prescribed a β -blocker and the doses of ACE-Is and β -blockers used were lower than those proven to be effective in large controlled clinical trials. Therefore, lack of similarity between patients with heart failure in clinical practise and those in clinical trials does not adequately explain under-utilization of therapy.

It is in keeping with earlier reports that a minority of heart failure patients in clinical practise would have qualified for participation in landmark RCTs.^{21–27} It should be noted, however, that the absence of a quantitative measurement of the LV function and the failure to prescribe ACE-Is excluded many patients from being considered trial eligible. As only few patients fulfilled all clinical trial criteria, we also tried to identify the maximum potential numbers of patients who should receive an ACE-I and β -blocker (i.e. those with evidence of LVEF, without contraindications like renal failure or asthma). Treatment of these patients compared with trial-eligible patients revealed only minor differences with respect to ACE-Is and β -blockers. Aldosterone antagonists, however, were given more frequently in trial-eligible patients.

This analysis shows that the under-representation of women in heart failure trials^{23,24} is partly explained by the use of a low LVEF as an inclusion criterion and the higher prevalence of preserved LVEF among women. To increase the proportion of women in heart failure trials, it would be necessary to introduce bias in favour of recruiting women or relax the LVEF entry criterion. This analysis also reveals that the exclusion of patients with preserved left ventricular function (PLVF) and those with renal dysfunction is an important reason for the average of patients in trials being about a decade younger than the epidemiological population.^{21–23} Indeed, in CHARM preserved,²⁹ which recruited only patients with PLVF, the proportion of women was substantially higher and the patients somewhat older than those in other RCTs of heart failure.

The limited generalizability of the results of RCTs is widely recognized. Trials with more varied enrolment criteria are required to provide information on the complete scope of a disease and its treatment to extend generalizability. This



*) Number of contra-indications, used in the analysis.
 ‡) Percentage is based on total survey population.

Figure 1 Flow diagram illustrating the proportion of trial-eligible patients.

Table 2 Baseline characteristics of patients enrolled in the Euro Heart Survey on Heart Failure

	Total	Trial-eligible (pooled)	Trial-ineligible (pooled)	Other survey patients ^b	P-value
<i>n</i>	10701	1346 ^a	6595	2760	
Age [median (25th–75th)]	73 (64–80)	67 (57–74)	74 (64–82)	74 (66–79)	<0.001
Gender (women) (%)	5020 (47)	342 (25)	3207 (49)	1471 (53)	<0.001
Co-morbidity (%)					
Hypertension	5679 (53)	636 (47)	3534 (54)	1509 (55)	<0.001
Diabetes mellitus	2907 (27)	355 (26)	1723 (26)	829 (30)	<0.001
Ischaemic heart disease	6419 (60)	841 (63)	4246 (64)	1332 (48)	<0.001
Acute coronary syndrome ^a	2883 (27)	166 (12)	2505 (38)	212 (8)	<0.001
Valvular heart disease ^a	768 (7)	41 (3)	677 (10)	50 (2)	<0.001
Renal insufficiency ^{a,c}	1163 (11)	82 (6)	974 (15)	107 (4)	<0.001
Pulmonary disease	2876 (27)	245 (18)	1701 (26)	930 (34)	<0.001
Severe pulmonary disease ^a	1743 (16)	188 (14)	971 (15)	584 (21)	<0.001
Prior/current stroke	939 (9)	83 (6)	541 (8)	315 (11)	<0.001
Chronic atrial fibrillation	2482 (23)	284 (21)	1520 (23)	678 (25)	0.04
Cancer ^a	1058 (10)	0 (0)	1058 (16)	0	—
LVEF known (%)	5311 (50)	1346 (100)	3965 (60)	0	—
LVEF [median (25th–75th)] ^d	41 (30–55)	29 (22–33)	48 (40–60)	—	<0.001
Pharmacological treatment (%)					
ACE-Is	6610 (62)	1158 (86)	3595 (55)	1857 (67)	<0.001
β-Blockers	3744 (37)	650 (48)	2584 (39)	710 (26)	<0.001
Cardiac glycosides	3825 (36)	622 (46)	2147 (33)	1056 (38)	<0.001
Diuretics	9297 (87)	1241 (92)	5521 (84)	2535 (92)	<0.001
Aldosterone antagonists	2197 (21)	522 (39)	1135 (17)	540 (20)	<0.001

^aMajor exclusion criteria of the selected trials, as shown in Table 1.^bPatients without major exclusion criteria, but without known LVEF.^cCreatinine ≥ 177 μ mol/L or ≥ 2.0 mg/dL.^dOnly in patients with known LVEF.**Table 3** Patient characteristics and pharmacological treatment of trial-eligible patients enrolled in the EHS on Heart Failure

	SOLVD-eligible	MERIT-HF-eligible	RALES-eligible	Pooled RCTs ^a	Trials
<i>n</i>	1005	507	782	8223	1–3
Age [median (25th–75th)]	65 (55–72)	67 (57–73)	68 (58–75)	63	1–3
Female gender (%)	224 (22)	141 (28)	179 (23)	1848 (22)	1–3
Non-excluding co-morbidity (%)					
Hypertension	447 (45)	254 (50)	382 (49)	2835 (43)	2,3
Diabetes mellitus	262 (26)	140 (28)	207 (27)	1647 (25)	2,3
Chronic atrial fibrillation	212 (21)	104 (21)	166 (21)	689 (14)	2,3
Prior myocardial infarction	463 (46)	229 (45)	409 (52)	3611 (55)	2,3
Prior coronary intervention	216 (22)	106 (21)	139 (18)	—	—
Pharmacological treatment (%)					
ACE-Is					
Treated	829 (83)	472 (93)	782 (100)	6714 (91)	1,3
$\geq 50\%$ of target dose	605 (60)	337 (67)	564 (72)	—	—
\geq target dose	408 (41)	231 (46)	375 (48)	—	—
β-Blockers					
Treated	489 (49)	272 (54)	357 (46)	371 (9)	1,2
$\geq 50\%$ of target dose	172 (17)	102 (20)	129 (17)	—	—
\geq target dose	54 (5)	29 (6)	44 (6)	—	—
Cardiac glycosides					
Treated	484 (48)	260 (51)	373 (48)	5479 (67)	1–3
Diuretics					
Treated	900 (90)	507 (100)	782 (100)	7463 (91)	1–3
Aldosterone antagonists					
Treated	418 (42)	213 (42)	334 (43)	—	—

For ACE-Is the daily target doses were defined as 75 mg for captopril, 20 mg for enalapril, 5 mg for ramipril, 5 mg for lisinopril, and 4 mg for perindopril. For β-blockers these doses were 150 mg for metoprolol, 50 mg for atenolol, 50 mg for carvedilol, and 10 mg for bisoprolol.

^aData based on results as presented in the main articles of the three RCTs (1, SOLVD; 2, MERIT-HF; 3, RALES).

Table 4 Twelve-week mortality of hospital survivors in relation to target doses

Subpopulation	Treatment	Target dose (%)	n	Follow-up mortality	P-value
SOLVD-eligible	ACE-Is	≥50	600	24 (4.0)	0.002
		<50	379	33 (8.7)	
MERIT-HF-eligible	β-Blockers	≥50	102	3 (2.9)	0.04
		<50	399	35 (8.8)	
Trial-ineligible (pooled)	ACE-Is	≥50	2367	102 (4.3)	<0.001
		<50	3671	317 (8.6)	
	β-Blockers	≥50	1224	47 (3.8)	<0.001
		<50	4814	372 (7.7)	

has happened with ACE-Is over the last 15 years. Trials in post-infarction patients with LVSD and in patients with vascular disease without heart failure suggest that the benefits of ACE-Is may be generalizable, although no trials have shown morbidity or mortality benefit in patients with PLVF as yet. ACE-Is have a well-recognized side-effect profile and are well tolerated.³⁰ Similarly, trials of β-blockers have shown benefit in patients with heart failure and LVSD and in patients who have had a myocardial infarction. The SENIORS³¹ and a smaller study of propranolol³² suggest that β-blockers are effective even in elderly patients, regardless of the LVEF. A recent analysis of patients in this survey revealed that patients treated with ACE-Is or β-blockers, irrespective of the LVEF, had a better survival than those who did not.³³

Treatment with aldosterone antagonists is based on only two clinical trials, RALES and EPHESUS,^{9,10} and more RCTs are desirable to increase generalizability. Achieving the equipoise between the ethics of withholding a treatment that has shown striking reductions in mortality against the desire to demonstrate generalizability may be difficult but important to demonstrate safety and efficacy in wider clinical practise.^{34,35}

Although adherence to guidelines is encouraged by national and international societies, not all patients will or should be treated as advocated in the guidelines. Guidelines only provide the general principle of how a patient should be treated; they do not address every individual patient's clinical problem. Management of individual patients is more complex than simply following the guidelines, as contraindications, individual reactions to the medication side-effects, co-morbidity, and subsequent multiple co-medications as well as the treatment goals for the individual patient can affect management decisions.^{27,36} However, this survey suggests that there is a shortfall in effective therapy, even when patients in clinical practise fulfil the criteria of landmark clinical trials of heart failure treatment.

These observations raise the question why a sizable proportion of patients were not treated according to evidence-based guidelines. Identified barriers in following clinical guidelines, such as lack of awareness, lack of agreement with the guidelines, difficult to use (not concise enough), no motivation to change current practise, as well as economic pressure to limit the costs, and so on, might partly explain the limited adherence to guidelines in clinical practise.^{29,30,37} These barriers imply that more effort is needed to improve guideline adherence. It is acknowledged that initiation and up-titration of these drugs require careful, repeated assessment to monitor individual

responses. Especially in the case of β-blockers, treatment can provoke initial worsening. Concerns that initiation of a β-blocker too early during hospitalization could destabilize the patient³⁸ should also be taken into account when trying to explain why physicians were unable to initiate evidence-based therapy. Regarding up-titration of ACE-Is and β-blockers, it should be noted that this requires an effective heart failure follow-up program, as it is to be expected that the majority of patients are not hospitalized during this phase. Conversely, some have advocated that fixed target doses may not be optimal for individual patients.¹⁸ In addition to this, doctors may be satisfied with a symptomatic improvement already with smaller doses of drugs and not push for higher targets to avoid adverse events. Thus, smaller doses than recommended can and should not generally be regarded as suboptimal therapy. In our survey, however, the underlying reason for choosing dosage cannot be reliably analysed. The clinical trial evidence indicating that target doses of ACE-Is and β-blockers are more effective than lower doses is sparse. Randomized controlled trials do suggest that higher doses of ACE-Is may be more effective.^{39–41} There is less evidence that the dose of β-blocker is important.^{42,43} However, a beneficial effect in patients who were treated with at least 50% of the doses used in RCTs, compared with patients who received less, was observed in this survey. It should be noted, however, that most of the evidence for benefit is based on titration to target doses recommended by landmark trials.

Limitations

As most hospitals volunteered, it is possible that the observed pharmacological treatment was even better than in every day clinical practise, because they were energetic in implementing existing evidence. In selecting trial-eligible patients, we focused on the most important entry criteria for the trials but did not include every detail. Finally, it is possible that some of the under-utilization of β-blockers reflects the fact that the patients had recently been hospitalized. At the time of the survey, it was generally recommended to stabilize patients first, before initiating β-blockers.

Conclusion

Only a minority of patients with heart failure would be eligible for participation in the majority of randomized controlled trials of heart failure. This reflects the general exclusion of patients with PLVF and, to a lesser extent,

renal dysfunction. Among patients who fulfilled the key enrolment criteria of selected landmark trials, ACE-Is, β -blockers, and aldosterone antagonists were under-utilized. This survey, however, gave no clues for the reason of under-utilization.

Conflict of interest: no conflict of interest with respect to this manuscript.

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